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Regenerative Potential of Intra-articular BMAC in Mild to Moderate Knee Osteoarthritis: A Clinical Evaluation

Ankit Batra[1], Rajni Ranjan[1], Rakesh Kumar[1], Nishant Manhas[1], Somoshree Sengupta[2], Shuvojit Moulik[3]*

[1]Department of Orthopaedics, School of Medical Sciences & Research, Sharda University, Greater Noida, Uttar Pradesh, India, [2]Academy of Scientific and Innovative Research, AcSIR Headquarters CSIR-HRDC Campus, Postal Staff College Area, Sector 19, Kamla Nehru Nagar, Ghaziabad, Uttar Pradesh, 201002, India, [3]Department of Biomedical Research, Santosh Deemed to be University, No.1, Santosh Nagar, Pratap Vihar, Ghaziabad, Uttar Pradesh, 201009, India. *Corresponding Author's Email: shuvojitmoulik.crf@santosh.ac.in

Abstract

Osteoarthritis (OA) is a common, degenerative joint disease that impairs function and causes severe pain and stiffness. Only symptomatic alleviation is provided by current conservative therapies, which do not change the joint biochemistry or the normal course of OA. Rich in growth hormones and mesenchymal stem cells, bone marrow aspirate concentrate (BMAC) offers a promising regenerative treatment to encourage tissue repair and reduce inflammation. Clinical evidence for BMAC in OA is still inconclusive. The clinical effectiveness of a single intra-articular BMAC injection for pain management and functional improvement in primary knee OA was assessed in this prospective interventional trial, which ran from January 2021 to June 2022. An autologous BMAC injection of 10 mL was given to 25 patients (aged 45–80) with Kellgren-Lawrence grades I–III OA. The BMAC was made from iliac crest aspirate using standardized centrifugation. The Visual Analogue Scale (VAS) was used to measure pain, and the Oxford Knee Score (OKS) was used to measure function at baseline, one, three, and six months after the treatment. Improvements were statistically significant, according to the results. At six months, the mean VAS ratings dropped and the average OKS scores increased. Although 8% of patients experienced edema and 20% reported temporary pain (≤2 weeks), the surgery was well tolerated. According to these results, mild to moderate knee OA can be safely and effectively treated with a single BMAC injection in the short to medium term. This suggests that additional large-scale, controlled trials are necessary to confirm the treatment's promise.

Keywords: Bone Marrow Aspirate Concentrate, Knee, Mesenchymal Stem Cells, Osteoarthritis, Pain, Regenerative Medicine.

Introduction

Osteoarthritis (OA) is the most common chronic degenerative disease of synovial joints, characterized by the progressive loss of articular cartilage and other changes in the joint, including inflammation of the synovium, remodeling of the subchondral bone and formation of osteophytes (1, 2). Painful stiffness and progressive functional limitation can lead to disability (3). Globally, there is a large burden of OA, estimated to affect around 3.3 – 3.6 percent of the world's population, and to be one of the main causes of disability (4). More than 43 million people have some degree of moderate to severe functional limitation due to OA (5). Currently, treatments available for moderate to severe knee OA are mainly symptomatic based and aimed at managing symptoms rather than modifying the disease process. The limitations of currently available treatments emphasize a need for a new type of therapy that can halt the progression of disease and restore joint homeostasis. Interest in using regenerative medicine to develop disease halting treatments for OA has been stimulated by the identification of a class of stem cells called mesenchymal stem cells (MSCs). MSCs are a class of multipotent stromal cells that can differentiate into all types of mesodermal cells (e.g., cartilage, bone, fat) and have a high level of self-renewal (6). It is now established that MSCs do not exert their therapeutic effects by differentiating into the damaged tissues within the OA joint but instead by releasing a variety of signaling molecules (i.e., growth factors, cytokines and chemokines) that modulate the local micro-environment within

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the OA joint and promote endogenous repair processes (7). These signaling molecules released by MSCs have been shown to reduce inflammation, reduce the activity of catabolic enzymes, and inhibit the activity of pro-inflammatory cytokines, thereby reducing joint destruction and pain (7). A practical and commonly used autologous source of MSCs for use in clinical applications is bone marrow aspirate concentrate (BMAC).

There is a growing body of evidence indicating that intra-articular injections of BMAC may result in reduced pain, improved functional status, and potentially, the promotion of tissue repair in the OA joint (8). BMAC is a complex mixture of cellular and non-cellular components derived from the bone marrow of a patient undergoing bone marrow aspiration. Following the concentration of the bone marrow via centrifugation, the final product is composed of a heterogeneous cellular population including platelets, white blood cells, hematopoietic progenitors and a small number of MSCs (typically less than .01%) (8). While the majority of the therapeutic effects of BMAC are thought to be derived from the growth factor-rich secretory products of the MSCs contained within the product (i.e., the secretome) (8), BMAC is also rich in a wide variety of anabolic growth factors, including members of the TGF-β superfamily, PDGF, IGF-I, FGF-18 and BMP-2 and BMP-7 (9). Importantly, BMAC has been demonstrated to contain much higher concentrations of IL-1Ra than PRP, which would theoretically allow it to counteract the pro-inflammatory and catabolic actions of IL-1β, a key mediator of the OA disease process (10). Collectively, the multitude of components present within BMAC allows it to modulate several pathways: promoting the production of the extracellular matrix and the differentiation of chondrocytes, suppressing the action of pro-inflammatory cytokines (IL-1β and TNF-α), and stimulating the remodeling of the subchondral bone to produce a more favorable environment for the OA joint (11).

Recent advances in our understanding of MSC-based therapies have shifted the paradigm from direct cell replacement to a "hit-and-run" paracrine model, in which the injected cells serve temporarily as a "mini-pharmacy," releasing anti-inflammatory, immunomodulatory, and trophic factors that have a lasting effect on the joint environment without needing to become permanently integrated (12).

Although there is a strong biological rationale supporting the use of MSCs to treat OA, and although preliminary data indicate that MSCs are beneficial in treating OA, the existing literature indicates that the results of BMAC administered intra-articularly for the treatment of knee OA are highly variable. This variability is largely due to the great deal of heterogeneity seen in the preparation methods, cell dosing, injection volumes and patient populations studied in the existing literature. Thus, the exact efficacy and ideal method of delivery of BMAC remains unknown. To help address this question, the present study was conducted to evaluate the clinical efficacy of a single well-defined dose of intra-articular BMAC in patients with primary knee OA and assess the outcomes of pain and physical function.

By providing consistent methodologies and data regarding outcomes, this single arm study hopes to provide a foundation upon which subsequent studies evaluating the efficacy of BMAC for knee OA can build, ultimately leading to the establishment of standardized protocols for future comparative studies to establish whether BMAC is an efficacious treatment for knee OA.

Materials and Methods

Materials

The materials used in preparation of the Bone Marrow Aspirate were the standard 11-gauge Jamshidi ™ bone marrow biopsy/aspiration needle (BD, Becton, Dickinson and Company, USA), and a sterile 1 mL syringe containing liquid heparin sodium (1000 IU/mL, Neon Laboratories Ltd.), which served as an anticoagulant and prevented coagulation. The processing and concentrating of the autologous aspirate was conducted with sterile 50 mL disposable conical centrifuge tubes (Falcon, Corning Incorporated, USA) and a clinical tabletop centrifuge (for example, REMI R-8C Benchtop Centrifuge, REMI Elektrotechnik Ltd., India) that had been calibrated to run for 2.5 minutes at exactly 3800 rpm. Subsequently, sterile 10 mL syringes and 22-gauge intra-articular needles (BD Microlance, Becton, Dickinson and Company) were used to conduct the final 10 mL infiltration of the 10 mL BMAC product into the affected knee joint.

Study Design and Duration

This research was executed as a preliminary, single-arm interventional trial and lasted 18 months, beginning in January 2021 and concluding in June 2022. As noted in the title, this research report is "a prospective interventional study", but it is also a single-arm study by design, and therefore, it does not have a concurrent control group (i.e. placebo, saline, and/or active treatment group), and thus meaning that any improvements in pain and function cannot be exclusively ascribed to BMAC intervention. The placebo effect, a natural history of the disease (especially as it relates to early stages), or post injection report of movement and activity could provide benefit or outcomes towards the improvements experienced. This is an important consideration in approaching the discussion section, which takes these limitations of design into consideration. It also useful for suggesting future research designs including RCTs as the gold standard for both developing and determining efficacy.

Study Population: Inclusion and Exclusion Criteria

The study sample comprised 25 patients who were included in the study with certain diagnostic and exclusion criteria so that a relatively homogenous group could be used to evaluate the effectiveness of BMAC. The patients presented with primary, OA of the knee, defined for study inclusion as Kellgren-Lawrence (K-L) grade I to III. Patients had to be between the ages of 45 - 80 years, without a preference for male or female patients.

There were several screening exclusion criteria to help reduce any potential variance for an otherwise variable outcome, and also to safeguard patient safety. Patients were excluded if they had OA that was post-traumatic, previous knee surgeries, active infection, uncontrolled diabetes mellitus, any rheumatological or other systemic diseases, or any malignancy. Patients taking any immunosuppression drugs, current NSAID and/or steroid therapy, or had an intra-articular steroid injection in the past 3 months were also excluded.

As highlighted by the researchers, the inclusion and exclusion criteria (K-L I-III, targeted age range, and excluded comorbidities such as diabetes, systemic diseases, and recent steroid/NSAID use) aimed at increasing the internal validity of the study. A highly specific and homogenous group of participants were selected to reduce the number of variables that might otherwise mask the direct effect of BMAC treatment. Naturally, such rigor for evaluating the effectiveness of this intervention is at the expense of external validity. The study shows that BMAC works in a defined group of patients. The way this group was defined limits how broadly we can interpret the study's results. As such, it is unclear whether the study's results will be applicable to other larger groups of clinical patients. For example, the study excluded individuals with severe osteoarthritis (K-L grade IV) as well as those with post-traumatic osteoarthritis. Additionally, the study excluded many average patients with common comorbid conditions that would necessitate the use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Therefore, additional research is needed to assess the effectiveness of BMAC in patients from various demographic backgrounds. In future studies, researchers could enroll patients with higher K-L grades and/or those who have well-controlled co-existing medical conditions.

BMAC Preparation and Intra-articular Injection Procedure

The entire procedure for BMAC preparation and injection was meticulously performed within the operating theatre (O.T.) complex, strictly adhering to sterile techniques at every step.

Bone Marrow Aspiration

The patients were placed supine on the table. Standard asepsis was obtained in the skin over the lateral aspect of the pelvis. An iliac crest puncture was made under local anaesthesia, aspirating a total of 30 mL of bone marrow into syringes containing 1 mL of heparin to prevent coagulation.

BMAC Concentration

The aspirated bone marrow was placed in a first disposable cylinder and immediately centrifuged for 2.5 minutes at 3800 rpm. The aspirate separated into 3 distinct layers after centri-fugation: a platelet plasma suspension, an early buffy coat (containing concentrated nucleated cells, including MSC's), and a red cell layer. The top plasma layer and 2 mL of the buffy coat were aspirated and then moved to a second disposable cylinder. The BMAC buffy coat was then reconstituted into the plasma by simply swirling to produce approximately 10 mL of concentrated BMAC (13).

Intra-articular Injection

The 10 mL of the final BMAC product was infiltrated into the infected knee joint within 30 minutes of preparation. The injection was given starting at the lateral joint line towards the intercondylar area.

Post Injection Care

After the injection the joint was passively mobilized for uniform distribution of the BMAC throughout the intra-articular space. Patients were allowed full weight bearing status with encouragement for the return to light activities as tolerated. We instructed patients to keep weight bearing and to remain off oral NSAIDs, oral corticosteroids, and perform ice fomentation for the knee for three days (14). Generally, patients were able to resume full activity within 6-weeks. We did not prescribe any additional therapies, such as bracing, and recorded all adverse events/complications.

The detailed descriptions of BMAC, the aspirate (30 mL), centrifuge (2.5 minutes at 3800 rpm), and final product (10 mL), would be beneficial for reproducibility in the context of this study. The very next "Review of Literature" section states the following: "Some of the commercially available systems provide rapid centrifuge times from 7.5 to 20 minutes, speeds from 2400 to 4000rpm or even requiring multiple spins (15). The output volume of BMAC can be variable, and can range from 3 to 40 mL". These factors illustrate one of the primary challenges for the transfusion of the derived BMAC: no clear standardization. Although our study gave a specific protocol, it was not the global best approach or an "optimal" technique. This offers a difficult scenario for experimentation in the understanding of biological potency and clinical outcomes when transferring processes. Not only the cell yield, or, growth factors concentrations (in the final BMAC), were also not reported. Thus, to then further compare the "dose", is even more complicated. This suggests future inquiry should not only involve clinical trials of the BMAC, but to concurrently phenotype the biological characteristics (such as MSC count, viability, growth factor profile) of the BMAC as well. This will yield correlation of attributes of specific BMAC and links to clinical outcomes, and will support the development of future standardized BMAC procedures.

Follow-up Schedule and Outcome Measurements

Patient outcomes were systematically assessed at multiple time points: pre-procedure (baseline) and then at 1, 3, and 6 months post-injection.

Outcome Measures

The Visual Analogue Scale (VAS) which measure the pain severity was quantified using the Visual Analogue Scale, a widely accepted and validated tool for subjective pain assessment (16). The Oxford Knee Score (OKS) which was a functional status of the knee joint was evaluated using the Oxford Knee Score, a self-administered questionnaire specifically designed for knee-related conditions (17). The OKS comprises 12 items, with a maximum possible score of 48, where a higher score indicates superior knee function.

The selection of VAS and OKS is appropriate as they are validated, patient-reported outcome measures that capture both pain and functional aspects, which are the primary concerns for OA patients. The 6-month follow-up period allows for an initial assessment of the intervention's short-to-mid-term efficacy and durability. However, for a chronic and progressive disease like OA, a 6-month follow-up is relatively short. It provides strong evidence for immediate and early sustained benefits but cannot conclusively demonstrate long-term disease modification or the prevention of future surgical needs. The thesis itself acknowledges this, stating the need for longer follow-up for a "better understanding". While the chosen outcome measures and follow-up schedule are suitable for a preliminary study, the necessity of extended follow-up periods (e.g., 1-2 years or more) in future research is crucial for evaluating the sustained efficacy of BMAC, its potential to truly alter the disease's natural history, and its long-term impact on patient management and quality of life.

Statistical Analysis

The study aimed for a sample size of 25 patients. This was determined based on a 95% confidence level, a z-value of 1.96, and an estimated confidence interval/margin of error of +/-20%. Assuming a p% of 28.7% and q% of 72%, the calculated sample size was 20. Accounting for a 10% non-response rate, the total sample size was set at 25.

Data Collection and Analysis

Data were collected manually, meticulously tabulated in an MS Windows Excel sheet, and subsequently analysed using GraphPad PRISM 10.6.1, employing a paired t-test to compare mean scores over time. While a sample size calculation is provided, a sample of 25 patients is inherently small for a clinical trial, especially in regenerative medicine where patient responses can be heterogeneous. A +/-20% margin of error is quite broad, suggesting that the study might be underpowered to detect smaller, yet clinically significant, effects or to confidently generalize findings to a larger population. This is a common characteristic of pilot or preliminary studies, as single-arm trials often have smaller sample sizes and shorter durations, which saves costs but limits evidence capacity. This limitation necessitates cautious interpretation of the findings as definitive proof of efficacy. The results are highly encouraging but require validation in larger, adequately powered studies to confirm generalizability and statistical robustness.

Ethical Considerations and Conflict of Interest

The study strictly adhered to ethical guidelines, ensuring that all participating patients received the standard of care. The study protocol received approval from the institutional ethics committee, ensuring compliance with ethical research standards. The authors declared no conflict of interest related to the present study.

Results

Demographic Characteristics of Study Participants

A total of 25 participants were included in the study. The mean age of the study participants was 57.20±8.32 years, with individual ages ranging from a minimum of 46 years to a maximum of 73 years. Most participants (48%, n=12) were in the 45-55 years age group, followed by 36% (n=9) in the 56-65 years group, and the remaining 16% (n=4) in the 66-75 years group as shown in Table 1.

Table 1: Distribution of Age Among the Study Participants (N=25)

Age	Frequency	Percentage
45-55	12	48
56-65	9	36
66-75	4	16

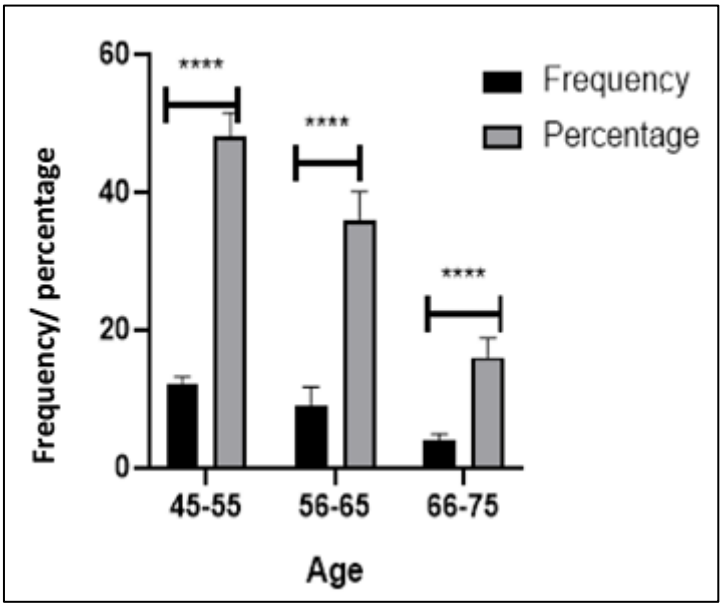

Figure 1: Distribution of Age Among the Study Participants (N=25)

Table 2: Distribution of Gender Among the Study Participants (N=25)

Gender	Frequency	Percentage
Female	18	72
Male	7	28

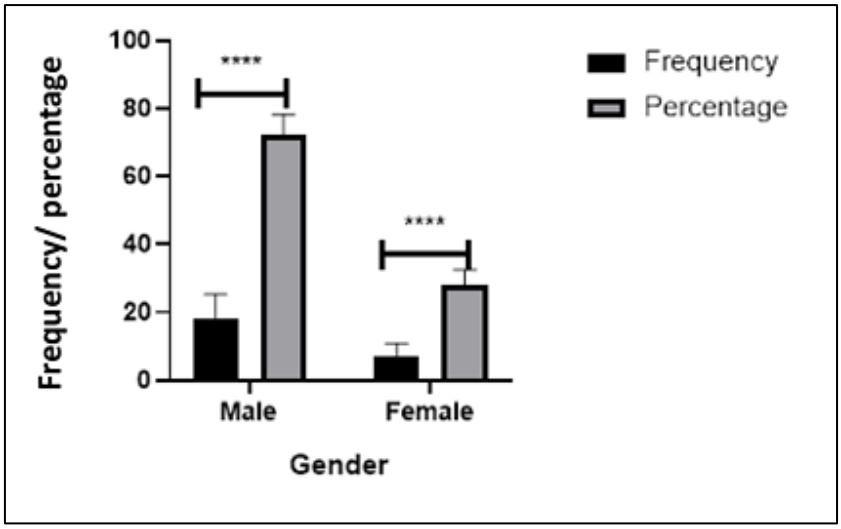

Figure 2: Distribution of Gender Among the Study Participants (N=25)

The study population exhibited a female preponderance, with 72% (n=18) being female and 28% (n=7) male in Figure 1. The distribution of gender has been presented in Table 2 and Figure 2. Based on the Kellgren-Lawrence (K-L) grading system, 40% (n=10) of participants had Grade 1 OA, 40% (n=10) had Grade 2 OA, and 20% (n=5) had Grade 3 OA. No participants with Grade 4 OA were included in Table 3 followed the data shown in Figure 3.

Table 3: Distribution of Duration of Disease in Months Among the Study Participants (N=25)

Duration (months)	Frequency	Percentage
4-8	12	48
9-12	7	28
13-16	4	16
17-20	2	8

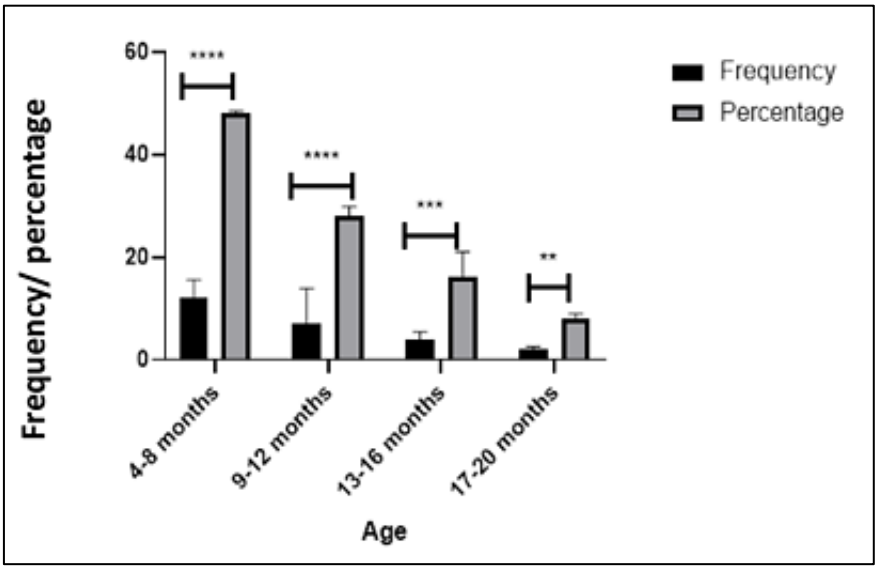

Figure 3: Distribution of Duration of Disease in Months Among the Study Participants (N=25)

The demographic profile of the study participants—mean age in the late 50s and a significant female preponderance—aligns consistently with the known epidemiology of primary knee osteoarthritis, which is more prevalent in older adults and women. The inclusion of K-L grades I-III, with a majority in grades 1 and 2, indicates a focus on early to moderate stages of the disease. This is clinically relevant as regenerative therapies are hypothesized to be most effective before extensive structural damage occurs. This demographic alignment suggests that the study

population is representative of a significant segment of OA patients who might be candidates for early, non-surgical interventions. This enhances the clinical applicability of the findings to a relevant patient group, despite the overall small sample size.

Table 4: Distribution of PreVAS Score Among the Study Participants (N=25)

Variable	Mean ± SD	Min	Max	Range
PreVAS	8.80±0.70	8	10	2
VAS 1st month	6.44±0.96	5	8	3
VAS 3rd month	4.96±0.84	4	6	2
VAS 6th month	1.72±0.68	1	3	2

Changes in Pain Scores (VAS) Over Time

The mean pre-procedure VAS score for pain was 8.80±0.70, with individual scores ranging from 8 to 10, indicating high baseline pain levels across the cohort as shown in Table 4.

At 1month post-injection, the mean VAS score significantly decreased to 6.44±0.96 (range 5-8). Further reduction was observed at 3 months, with the mean VAS score dropping to 4.96±0.84 (range 4-6). By 6 months, the mean VAS score had substantially decreased to 1.72±0.68 (range 1-3), indicating near-complete pain resolution for many participants. The reduction in VAS scores from baseline was statistically highly significant at all post-injection time points ($p<0.001$ for 1st, 3rd, and 6th months). The mean differences from pre-VAS were 2.36±0.86 at 1 month, 3.84±0.845 at 3 months, and 7.08±0.81 at 6 months as shown in Table 5.

Table 5: Association of Pre-VAS Score with Post VAS Scores Across the Months Among the Study Participants (N=25)

VAS Score	Mean difference ± SD	95% (confidence interval)	t (degrees of freedom)	p
1st month	2.36±0.86	(2.00, 2.71)	13.72 (24)	<0.001
3rd month	3.84±0.845	(3.48, 4.19)	22.57 (24)	<0.001
6th month	7.08±0.81	(6.74, 7.41)	43.57 (24)	<0.001

A reduction of over 7 points on the VAS scale (from 8.8 to 1.72) within 6 months is not just statistically significant but represents a profound clinical improvement (Table 5). In pain management, a 2-point or 30% reduction in VAS is often considered the minimum clinically important difference. This study's observed reduction far exceeds that threshold, indicating a substantial and tangible improvement in patients' daily pain experience. The progressive decrease in VAS scores over the 6-month period suggests a sustained, rather than transient, analgesic effect. The magnitude and consistency of pain reduction strongly support BMAC as a potent therapeutic option for alleviating knee OA pain, potentially reducing the need for long-term analgesic medication and improving overall patient comfort.

Changes in Functional Scores (OKS) Over Time

The mean pre-procedure OKS was 12.96±3.87, with scores ranging from 8 to 20, indicating considerable functional impairment at baseline (Table 6). At 1 month, the mean OKS significantly increased to 23.36±6.29 (range 12-32). By 3 months, functional improvement continued, with the mean OKS reaching 29.92±6.01 (range 20-40). At 6 months, the mean OKS further improved to 41.76±4.01 (range 36-48), nearing the maximum possible score of 48, which indicates excellent knee function.

Table 6: Distribution of PreOKS Score Among the Study Participants (N=25)

Variable	Mean ± SD	Min	Max	Range
Pre OKS	12.96±3.87	8	20	12
OKS 1st month	23.36±6.29	12	32	20
OKS 3rd month	29.92±6.01	20	40	20
OKS 6th month	41.76±4.01	36	48	12

The increase in OKS from baseline was statistically highly significant at all post-injection time points ($p<0.001$ for 1st, 3rd, and 6th months). The mean differences from pre-OKS were -10.40±4.32 at 1

month, -16.96±4.93 at 3 months, and -28.80±4.47 at 6 months as shown in Table 7.

The substantial increase in OKS from a mean of 12.96 to 41.76 signifies a dramatic improvement in knee function (Table 7), moving patients from significant impairment towards near-normal capabilities. This functional restoration directly translates into an enhanced quality of life, allowing individuals to engage more fully in daily activities, work, and social interactions that were previously limited by OA. The parallel improvement in both pain and function suggests a synergistic effect of the BMAC intervention, addressing both symptomatic and functional aspects of the disease. The robust functional improvements observed position BMAC as a promising therapy that can significantly restore mobility and independence in patients with early to moderate knee OA, potentially delaying or even obviating the need for more invasive surgical procedures.

Reported Complications

The study observed a low incidence of complications. Five participants (20%) reported localized pain at the injection site, and two participants (8%) experienced swelling (Table 8). Crucially, all reported pain and swelling resolved spontaneously within two weeks of the procedure, requiring no specific intervention beyond initial ice fomentation. No serious adverse events or long-term complications were noted throughout the 6-month follow-up period.

Table 7: Association of Pre OKS Score with Post OKS Scores Across the Months Among the Study Participants (N=25)

OKS Score	Mean difference ±SD	95% (confidence interval)	t (degrees of freedom)	p
1st month	-10.40±4.32	(-12.18, -8.62)	-12.03 (24)	<0.001
3rd month	-16.96±4.93	(-18.99, -14.92)	-17.17 (24)	<0.001
6th month	-28.80±4.47	(-30.64, -26.95)	-32.19 (24)	<0.001

Table 8: Distribution of Complications Among the Study Participants (N=25)

Complications	Frequency	Percentage
Pain	5	20
Swelling	2	8

The occurrence of only minor, transient complications (localized pain and swelling) that resolved quickly is a highly encouraging finding. This indicates a very favourable safety profile for the single intra-articular BMAC injection. Compared to the potential risks and side effects associated with long-term use of oral medications (e.g., gastrointestinal or cardiovascular issues with NSAIDs) or the inherent risks of surgical interventions, the safety profile of BMAC is a significant advantage. The minimal and transient nature of side effects enhances the attractiveness and patient acceptability of BMAC as a minimally invasive treatment option, particularly for patients seeking alternatives to conventional pharmaco-therapy or surgery. This low risk profile is critical for broader clinical adoption.

Discussion

This preliminary, single-arm interventional trial shows the substantial clinically relevant effectiveness of a single injection of Bone Marrow Aspirate Concentrate (BMAC) into the knee joint: pain improved considerably and clinically meaningful improvements in function were shown for patients with primary knee osteoarthritis (K-L Grades I-III) over a six-month follow-up. The improvements in Visual Analogue Scale (VAS) and Oxford Knee Score (OKS) were statistically highly significant and, more importantly, clinically meaningful.

The reduction in pain from a level of relatively high pain to minimal pain in just six months is clinically meaningful because a reduction in pain directly reflects increased patient comfort and therefore a reduction in the potential use of analgesic medications. At the same time, the dramatic increases in OKS scores (change from a mean of 19 to 44), showed remarkable, improvements in knee function, allowing patients to participate more fully in their daily activities and thereby improving their quality of life. The safety of the procedure was excellent, and only very minor local pain and swelling were reported, both of which were transient. The very low incidence of adverse events of the procedure reinforces the safety and tolerability of an autologous BMAC injection.

The simultaneous and significant improvements in both pain (VAS) and function (OKS) are more than additive; they are generally considered a synergistic effect that is significant for the successful management of OA. Less pain promotes more physical activity and ability to perform therapeutic exercises. The resulting physical activity and exercises can stimulate the periarticular muscles to strengthen, improve joint stability, and improve function. This positive feedback loop could just as easily help decrease pain and slow the progression of degenerative changes in the joint. The biological mechanisms underlying BMAC, including their anti-inflammatory and regenerative paracrine effects, which most likely initiate and maintain this virtuous circle resulting in total patient benefit. The dual benefit suggests that BMAC provides treatment for not only the primary symptom (pain) but also the primary consequence (functional limitation) of OA (8). This overall improvement has great value for patients, and indicates the potential break this cycle of progressive decline we traditionally observe with symptom focused treatments.

Our statistically significant decrease in the VAS scores and statistically significant improvement in the OKS scores is supportive of the successful outcomes that have been reported in several other studies examining BMAC. The 6-month mean VAS of 1.72 is similar to the mean of 1.5 (18) and the average of 6.7 (19) for similar time points but the former study was an observational trial. Even the OKS improving to 41.76 at 6 months compares favourably to 32.29 (20). These similarly consistent results across studies with method-logical differences further substantiate the therapeutic action of BMAC (8).

The minor, transient complications reported (20% pain, 8% swelling) in this study is consistent with the safety profile in the literature that supports BMAC is safe despite having been reported adverse events. A study reported minor complications at similar rates (26.3% pain, 5.2 % swelling) (21). The absence of serious adverse events is an indicator that BMAC is safe (22-25).

While the introduction referenced "conflicting results secondary to the differences and/or inconsistencies in methodologies", the robust detailed comparisons in the discussion illustrate that the results of this study (demographics, pain, function, safety) are actually "comparable with other study results". This paradox demonstrates that despite a variation in preparation routes, the clinical efficacy and safety profiles of BMAC are consistent across all studies for patients with early to moderate OA. The consistency of clinical efficacy and safety profiles suggest that BMAC has a basic therapeutic effect that will be recognized in the clinic regardless of how it is prepared or studied (8). This is substantial as the weight of evidence for BMAC continues to grow stronger and may be pointing to a benefit beyond being a by-product of a specific protocol with the biological changes being consistent across different studies. This pattern highlights the need for future meta-analyses which can more systematically assess methodological heterogeneity to reach a more certain conclusion and determine optimal treatment conditions.

The results from this study indicate that BMAC therapy may have important implications for the non-surgical management of mild to moderate knee osteoarthritis. The substantial pain relief delivered can greatly enhance patients' comfort in their daily life and can ultimately decrease the need for prolonged use of conventional analgesics with the attendant adverse effects. Further, the dramatic improvements in functional outcomes observed indicate BMAC can restore patients' mobility and improve their ability to perform activities or daily living which will improving quality of life overall.

Most importantly, results of the study combined with prior knowledge of the biological nature of BMAC and its MSC-mediated anti-inflammatory and regenerative paracrine or local effects, imply a potential for BMAC to go beyond symptom relief and potentially slow the degenerative process of cartilage. If this assumption is correct, BMAC may represent a paradigm shift from acceptable chartered palliative care to an improved disease-modifying process that yields satisfactory, efficient and possibly lasting results. As a non-invasive, autologous treatment with little risk, BMAC with stem cell enriched therapy is a potential early intervention protocol that may be able to delay or even prevent invasive alternatives such as total knee arthroplasty in younger patients or patients in the mild to moderate stages of OA.

The most significant implication of the BMAC treatment, may be the possibility of a departure

from symptomatic management of the condition to actual disease modification. Although this 6-month study cannot prove long-lasting structural changes, the significant clinical improvements noted (pain, function), associated with known biological mechanisms of BMAC (cartilage regeneration, an anti-inflammatory role, subchondral bone remodelling) imply a potential capacity to influence the progression of the disease. If BMAC can slow degeneration, a powerful non-surgical alternative may remain available, that would be able to delay or totally negate the need for total joint replacement surgery and therefore improve patient outcomes and lower health care costs long term. The implication of disease modification and surgical delay would be a significant step forward in OA treatment. It would serve as an important reason to include BMAC therapy in early intervention treatment plans for patients who are not yet surgical candidates and for individuals who would like to avoid surgery.

Conclusion

Within a cohort of patients with mild to moderate primary knee osteoarthritis, a single intra-articular injection of Bone Marrow Aspirate Concentrate (BMAC), resulted in statistically and clinically significant improvements in both pain reduction and functional outcomes at 6 months post-injection compared to baseline. The BMAC was well tolerated with no serious adverse reactions occurring throughout the course of the study; thus, these data further support the notion that BMAC is a safe intervention. Although our results support the use of BMAC as an alternative, but safe, and potentially effective short- to mid-term symptomatic treatment option for patients with symptomatic knee OA, there are many limitations to this study that need to be acknowledged. Firstly, the lack of either a comparison group or a placebo control group precludes making a definitive conclusion regarding the cause-and-effect relationship between the BMAC and the observed clinical improvement; hence, we cannot rule out the contributions from natural fluctuation of the disease and/or the placebo effect as contributing to the observed clinical improvements. Second, although theoretically BMAC may provide a means to slow the degenerative process of cartilage, we can make no such claims based upon the results of this study, since we did not have access to either objective structural imaging data or to biochemical/biological proof of the effects of the BMAC. Lastly, the fact that we demonstrated significant clinical improvement through 6 months post-BMAC does not necessarily translate into sustained responses or disease modification; therefore, it will be necessary to perform studies of significantly greater duration to establish whether the benefits derived from the BMAC continue beyond the 6 months time frame. To obtain a better understanding of the long-term effectiveness of BMAC and to clearly establish its role in managing knee OA, future studies should be designed to include large-scale randomized-controlled trials with extended follow-up times and should incorporate both objective imaging and robust biological characterization.

Abbreviations

BMAC: Bone Marrow Aspirate Concentrate, BMP: Bone Morphogenetic Proteins, DMT: Disease-Modifying Therapeutic, K-L: Kellgren-Lawrence Grade, MSCs: Mesenchymal Stem Cells, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, OA: Osteoarthritis, OKS: Oxford Knee Score, PRP: Platelet-Rich Plasma, VAS: Visual Analogue Scale.

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Author Contributions

Ankit Batra: designed, planned the whole study, interpreted the data, Rajni Ranjan: writing, review, Rakesh Kumar: writing, review, Nishant Manhas: writing, Somoshree Sengupta: writing, Shuvojit Moulik: writing, supervision.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The corresponding author has access to all of the study's supporting data and results. Data will be provided upon request, taking legal and ethical requirements into account.

Declaration of Generative AI and AI Assisted Technologies in the Writing Process

The authors confirm that no technology aided by artificial intelligence (AI) was utilized in the creation of the manuscript.

Ethics Approval

This study was approved by the institutional ethics committee of Sharda University (Ref. No. SU/SMS&R/76-A/2020/107).

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